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Restless Legs Syndrome: From Diagnosis to Treatment

Huzursuz Bacaklar Sendromu: Tanıdan Tedaviye

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ABSTRACT

Restless legs syndrome (RLS) can be described by an urge to move limbs that typically coincides with an uncomfortable sensation. When at rest or inactivity, signs may start or develop worse; they usually go away when one moves or gets up for a walk. RLS can be both idiopathic or secondary to many kinds of health conditions, such as deficiency of iron, diabetes, obesity, hypothyroidism, and chronic renal failure. At the admission, secondary causes and iron tests, such as transferrin saturation and ferritin, must be evaluated. Assessments should be repeated when symptoms worsen, or when augmentation develops. Augmentation is a significant adverse effect of therapy by levodopa and dopamine agonists. More severe signs, early appearance of symptoms, and spreading of symptoms from the legs to other body parts are indicative of augmentation. Non-pharmacological treatments help some RLS patients control their symptoms. Iron-replacement therapy is a first-line treatment option for patients with indications of low body iron stores. The use of α2δ ligands as initial treatments instead of dopamine agonists has been recommended recently.
Keywords: Restless legs syndrome; augmentation; iron deficiency; iron therapy.

ÖZ

Huzursuz bacaklar sendromu (HBS), uzuvları hareket ettirme dürtüsünün tipik olarak rahatsız edici bir hisle örtüşmesiyle tanımlanabilir. Dinlenme veya hareketsizlik sırasında belirtiler başlayabilir veya daha kötü gelişebilir; genellikle kişi hareket ettiğinde veya yürüyüşe çıktığında kaybolurlar. HBS hem idiyopatik hem de demir eksikliği, diyabet, obezite, hipotiroidizm ve kronik böbrek yetmezliği gibi birçok sağlık durumuna sekonder olabilir. İlk başvuruda ikincil nedenler ve transferrin saturasyonu, ferritin gibi demir testleri değerlendirilmelidir. Semptomlar kötüleştiğinde veya augmentasyon geliştiğinde değerlendirmeler tekrarlanmalıdır. Augmentasyon, levodopa ve dopamin agonistleriyle yapılan tedavinin önemli bir olumsuz etkisidir. Belirtilerin daha şiddetli olması, belirtilerin erken ortaya çıkması ve belirtilerin bacaklardan diğer vücut bölgelerine yayılması augmentasyonun göstergesidir. Farmakolojik olmayan tedaviler bazı HBS hastalarının semptomlarını kontrol altına almasına yardımcı olur. Demir replasman tedavisi, vücut demir depolarının düşük olduğu belirtileri olan hastalar için birinci basamak tedavi seçeneğidir. Son zamanlarda dopamin agonistleri yerine başlangıç tedavileri olarak α2δ ligandlarının kullanılması önerilmiştir.
Anahtar kelimeler: Huzursuz bacaklar sendromu; augmentasyon; demir eksikliği; demir tedavisi.

INTRODUCTION

Restless legs syndrome (RLS), which is also referred to as Willis-Ekbom illness, was first identified by Sir Thomas Willis in 1685 (1). Later, in the mid-twentieth century, Karl Ekbom determined and described the syndrome further (2). The characteristic symptoms of RLS, a sensorimotor disease, include an urge to move an individual's legs, usually accompanied by an uncomfortable feeling (3). Symptoms with a circadian pattern begin or worsen at moments of resting or inactivity, and tend to be most severe in the late afternoon or early part of sleeping (4). RLS symptoms are usually experienced concurrently and on both sides in the deep muscles and bones of the lower extremities (5).

The quality of life and sleep of RLS patients can be seriously affected (6). Patients with RLS frequently seek medical advice due to insomnia. Furthermore, the severity of RLS can exacerbate symptoms of depression and decrease the quality of life. For this reason, it's important to recognize, prevent, and manage RLS symptoms. Previous studies demonstrated that the diagnosis is frequently missed and prolonged by years (7).

The aim of this review was to increase awareness about RLS diagnosis and treatments. Therefore, if medical professionals are more knowledgeable about RLS diagnosis and treatment, early identification and treatment of patients may be possible.

EPIDEMIOLOGY

RLS is a widespread disease that more commonly affects females than males with a prevalence of 5-10.6% (8-10). However, the average frequency of RLS is found to go up to 18-23% in the elderly (11). RLS has been shown to affect females 1.5-2 times more frequently than males in the majority of epidemiological studies (12). The results of the research indicate that RLS involves 3.6% of the Turkish population, with a relatively high prevalence in younger people (13).

PATHOPHYSIOLOGY

RLS pathogenesis is yet uncertain. Several hypotheses have been described, such as the impact of abnormal metabolism of iron, various neurotransmitters, and the primary opiate function (14). Radiology investigations demonstrated a link between the metabolism of iron with RLS, particularly in the nervous system (15). Whether low levels of iron in the central or peripheral nerve systems cause RLS remains a topic of debate (2). In a previous study, patients with RLS were shown to have decreased ferritin and increased transferrin levels of cerebral fluid (16). It has been shown that RLS severity increases by decreased peripheral iron levels, and the frequency of RLS has been reported to be higher in individuals suffering from iron deficiency anemia (17). Despite this, many RLS patients have normal serum ferritin levels (14). The current consensus suggests a cerebral iron shortage is an essential biological component of RLS, probably caused by a combination of variables such as low peripheral iron and/or genetics (18).

The rate-limiting enzyme in the production of dopamine, tyrosine hydroxylase, also needs iron as a cofactor (16). The pathological function of the dopaminergic system is supported by the significant relief of RLS symptoms with low doses of dopaminergic treatments. Studies haven't found any differences in CSF levels of dopamine between RLS patients and healthy controls, however (19). Investigations have demonstrated dopaminergic system abnormalities in RLS patients, particularly in the striatum. Dopamine signaling and dopamine receptor modulation are shown to decrease to their lowest level at night while increasing up to the highest level in the morning so-called circadian rhythm of dopamine (16). In addition to dopaminergic mechanisms, the pathophysiology of RLS has also been linked to endogenous opioids, glutamate/glutamine, and gamma-aminobutyric acid systems (1,11).

CLINICAL PRESENTATION AND DIAGNOSIS

RLS is identified by an urge to move the legs, unpleasant and uncomfortable sensations described as “twitching and wiggling”, “burning and itching”, “tingling and prickling”, “cramp”, “pins and needles”, “tickling sensation deep inside the muscles”, “electric shock sensations”, “prickling and pain” (20). RLS symptoms typically occur in both legs, but may start in one of the legs and subsequently spread to the other, or they may appear in the other leg on a separate day (21). However, RLS may be purely unilateral, as well. The features of RLS include an uncontrollable urge to move the lower extremities, occurring at rest or inactivity (21). At night, symptoms can occur or get worse compared to the daytime (2). The characteristics and diagnostic criteria of this sensorimotor phenomenon, updated in 2014 by the International Restless Legs Syndrome Study Group (IRLSSG) are summarized in Table 1 (11,21).

In addition to basic clinical criteria, RLS has 4 supportive characteristics such as periodic leg movements (PLMs), dopaminergic therapy response, family history of RLS, and absence of predicted sleepiness during the day that can support a diagnosis (2,21-23). Previous studies demonstrated that severe PLMs occur in approximately 80% of patients with RLS examined in clinical practice (2,22). Most RLS patients have at least some initial clinical relief from dopaminergic medications. When asked about their family members' history, 50 to 60% of patients with RLS indicate

Table 1. Diagnostic criteria for restless leg syndrome (11,21).

1. An urge to move the legs usually but not always accompanied by uncomfortable and unpleasant sensations in the legs
2. Symptoms begin or worsen during periods of rest or inactivity such as lying down or sitting
3. Symptoms are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. Symptoms occur or are worse in the evening or night than during the day
5. The occurrences of the above features are not solely accounted for as symptoms primary to another medical or behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

a relative of the first degree who has RLS signs (11). Patients may experience fatigue, reduced concentration, and depression as an outcome of sleep deprivation, but they do not report a level of daytime sleepiness (21).

RLS primarily affects the limbs. However, other body parts, including the mouth, neck, arms, face, abdomen, and genitals, have also been reported to be affected by RLS (21,22,24-27). The bodily parts most commonly affected were the legs, arms, trunk, head, neck, and genital region, in that order (28). When limb symptoms are absent, the involvement of other body parts can sometimes make a diagnosis difficult (28). There have been reports of atypical cases of RLS in which the legs show little or no impairment while the arms are primarily involved (27). Up to 50% of RLS patients experience upper-limb impairment, usually in those who experience more severe RLS symptoms (29). Additionally, "phantom" RLS cases have been documented when people who have had limbs amputated experience symptoms of RLS in the area where the missing limb was supposed to be (30).

For research and treatment planning, more homogeneous subgroups were defined. The definition of "intermittent RLS" refers to restless legs which, although less frequent than twice a week on average, are severe enough to need medical treatment (31). Generally, non-pharmacologic or intermittent medical therapies are recommended. Chronic persistent RLS occurs at least twice a week and is sufficiently severe to require daily medication. RLS that is resistant to monotherapy with appropriate doses of initial medicines because of side effects, augmentation, or effectiveness is known as refractory RLS (11).

COMORBIDITIES

Restless legs syndrome can be both idiopathic or secondary to many kinds of health. Secondary RLS, as compared to idiopathic RLS, usually begins over the age of 45 and progresses rapidly (32). Before the age of 45, RLS, is known as early-onset RLS, which is not closely related to blood levels of iron and progresses slowly with age. It is also common in family members (32). One of the most significant secondary causes of RLS is anemia due to iron shortage, for which the prevalence of RLS is reported as high as 25% to 35% (33).

Since, being a blood donor, pregnancy and end-stage renal disease are the potential risks for iron deficiency, these conditions are considered as the important contributors of secondary RLS (34). Regarding this, among 500 pregnant women, the prevalence of RLS is reported to be 17% for the first trimester, 27% for the second, and 30% for the third (35). Pregnancy-related symptoms can occur or get worse for a variety of reasons, such as iron and folate shortages, changes in hormones, and causes for vascular congestion in the legs (36). Patients who require dialysis due to end-stage renal illness also frequently experience RLS. Other conditions that are shown to be linked with RLS can be summarized as obesity, migraine, stroke, polyneuropathy, Parkinson's disease, hyperphosphatemia, obstructive sleep apnea, insomnia, anxiety, depression, emotion-focused coping with stress, and excessive daytime sleepiness, as well as narcolepsy (Table 2, 33-35). In addition, many drugs have been reported to aggravate or cause RLS, such as neuroleptics, antidepressants, antihistamines, lithium, and dopamine antagonists (37).

TREATMENT

Secondary causes of RLS should be evaluated and restored in the first step of treatment strategies of RLS. RLS symptoms may be reduced by treating some treatable comorbid conditions such as diabetes, obesity, hypertension, hypothyroidism, iron deficiency anemia, magnesium deficiency, and others. Iron stores should be evaluated both initial diagnosis of RLS and subsequently while long-term therapy. In addition, iron stores should be assessed in cases where there is a decreasing benefit from previously successful therapy, signs of augmentation, or a general clinical increase of symptom prevalence or intensity. Early in the morning following an overnight fast, serum ferritin, iron, percentage transferrin saturation, and total iron-binding capacity should all be assessed. It is recommended that oral iron therapy be tried for all RLS patients with serum ferritin concentrations of 75 mg/L or less and transferrin saturation levels of less than 45% (38). In cases when a more rapid response is required, oral iron cannot be adequately absorbed and tolerated, or if a three-month trial of oral iron use is inadequate to improve the symptoms of restless legs, intravenous iron therapy may be considered (38).

Many non-pharmacological therapies are beneficial in the treatment of idiopathic (primary) RLS. Massage, stretching, walking, cognitive distraction, and warm or cold baths are examples of the non-pharmacological therapy (11). These non-pharmacological treatments are

Table 2. Restless legs syndrome comorbidities (33-35)

Medical Disorders	Neurologic Disease	Medications
Iron deficiency	Parkinson disease	Antidepressants
Anemia	Multiple sclerosis	Neuroleptics
Blood donors	Stroke	Dopamine antagonists
Pregnancy	Migraine	Antihistamines
Renal failure	Narcolepsy	Lithium
Cardiovascular diseases	Polyneuropathies	
Obesity	Lumbosacral polyradiculopathies	
Diabetes mellitus		
Hypothyroidism		
Magnesium deficiency		
Obstructive sleep apnea		
Chronic obstructive pulmonary disease		
Rheumatoid arthritis		

generally tolerable and safe for all RLS patients and may help to avoid higher doses of medications.

Standard pharmacological medications for RLS are carbidopa/levodopa, non-ergot dopamine agonists, α2δ ligands, opioids, and benzodiazepines. The Movement Disorders Society Task Force provided a new set of guidelines in 2016 that encouraged the use of α2δ ligands as first-line treatment rather than dopamine receptor agonists (39). α2δ ligands have the potential to alleviate anxiety and insomnia in addition to treating chronic pain. A dopamine agonist is a better option when depression and weight gain are present, as α2δ ligands have the potential to cause these side effects (38).

The appropriate drugs are determined by categorizing the disease into intermittent, chronic progressing, and refractory subtypes. Thus, for patients with intermittent or mild RLS symptoms, only non-pharmacological treatment may be required (31). In addition, for individuals with intermittent or mild RLS, an appropriate monotherapy strategy may be the first line of treatment. Intermittent use of these medications may be helpful for RLS that occurs intermittently in the evening, at bedtime, or while waking up during the night, and for RLS related to specific activities. A once-daily dose of medication is recommended for those with chronic persistent RLS symptoms. However, for some patients to effectively treat unpleasant daytime symptoms, a divided dose with earlier daytime usage is also needed. In the case of refractory RLS, other exacerbating factors should be sought. Adding a second agent and trying to reduce the dose of the initial drug should also be considered. Further details on management approaches and algorithms can be found in the RLS Foundation consensus statement on RLS management (32,40).

Augmentation is a significant adverse effect of therapy by levodopa and dopamine agonists. Decreasing the dose of dopaminergic medications, or cessation of the drug is beneficial in managing augmentation. Augmentation syndrome (AS) is often seen in RLS patients who have been chronically treated by dopamine agonists. It was first described by Allen and Earley (41) in RLS patients. It is a worsening of RLS symptoms with temporally earlier, increasingly intense, and typically geographically ascending characteristics, which should be considered as an adverse effect of treatment. The Max Planck Institute criteria were used to determine the diagnostic criteria of augmentation that was revised in 2006 (Table 3, 42). The frequency of AS is highest with L-DOPA, which has a short half-life, and up to 73%, compared to 6-47% with pramipexole (43), and is related to the dosages and duration of treatment. Iron deficiency, high doses of dopaminergic therapy, particularly with a short half-life, the initial severity of RLS, long exposure to the treatment, advanced age, and a higher risk of self-medication are the risk factors for augmentation that are most frequently reported (44). It is important to differentiate augmentation from tolerance, early morning rebound, RLS progression, or fluctuations in disease severity, as well as neuroleptic-induced akathisia (45).

CONCLUSION

The quality of life and sleep are both significantly affected by RLS, a sensorimotor condition. The general model of the disease's pathophysiology, which includes iron, various neurotransmitters, and opiate pathways, continues to be studied. Most cases are idiopathic RLS. Secondary RLS has been associated with a higher incidence in populations at risk for iron deficiency, including blood donors, pregnant women, and patients with end-stage renal illness. The initial management approach should include measuring iron stores. The initial course of treatment with α2δ ligands has recently been proposed. Additionally, useful, dopamine agonists may cause augmentation.

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Table 3. Max Planck Institute criteria for the diagnosis of augmentation (42)

Augmentation requires criteria A + B, A + C or A + B + C to be met
A. Basic features (all of which need to be met) **1.** An increase in the severity of symptoms for at least 5 days a week **2.** No other factors explaining the aggravation **3.** There has been a prior positive response to treatment
B. A paradoxical response (although not immediate) to treatment: Symptoms worsen with increasing dose and better with decreasing dose
C. Earlier onset of symptoms. **1.** An earlier onset by at least 4 hours **2.** or symptoms start between 2-4 hours earlier in association with at least one of the following criteria compared to symptom status before treatment **a.** Shorter latency of symptoms at rest **b.** Spread of symptoms to other parts of the body **c.** Greater intensity of symptoms or increase in periodic limb movements via the polysomnography or immobilization test **d.** Shorter duration of relief from treatment

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